Defense Mechanisms

Host defenses against viruses fall into two major categories: (1) **nonspecific,** of which the most important are interferons and natural killer cells; and (2) **specific,** including both humoral and cell-mediated immunity. Interferons are an early, first-line defense, whereas humoral immunity and cell-mediated immunity are effective only later because it takes several days to induce the humoral and cell-mediated arms of the immune response.

Nonspecific Immune Defenses

The nonspecific immune defense mechanisms are activated immediately when pathogens penetrate the body's outer barriers. One of the most important processes in these basic defenses is phagocytosis, i.e., ingestion and destruction of pathogens. Granulocytes and natural killer cells bear most of the responsibility in these mechanisms. Changes in pH and ion balance as well as fever also play a role, for example, certain temperature-sensitive replication steps can be blocked. The most important humoral factor is the complement system. Interferons, which are described below, are also potent tools for fighting off viral infections.

Alpha and beta interferons are a group of proteins produced by human cells after viral infection (or after exposure to other inducers). They inhibit the growth of viruses by **blocking the synthesis of viral proteins.** They do so by two main mechanisms: One is a ribonuclease that degrades mRNA, and the other is a protein kinase that inhibits protein synthesis. Interferons are divided into three groups based on the cell of origin, namely, leukocyte, fibroblast, and lymphocyte. They are also known as alpha, beta, and gamma interferons, respectively. Alpha and beta interferons are induced by viruses, whereas gamma (T cell, immune) interferon is induced by antigens and is one of the effectors of cellmediated immunity. The following discussion of alpha and beta interferons focuses on the induction and action of their antiviral effect. Interferons inhibit the intracellular replication of a **wide variety** of DNA and RNA viruses but have little effect on the metabolism of normal cells. The selectivity arises from the presence of double-stranded RNA in virus-infected cells, which is not present in uninfected cells. Interferons have **no effect** on extracellular virus particles. Interferons act by binding to a receptor on the cell surface that signals the cell to synthesize three proteins, thereby inducing the **"antiviral state"**. These three proteins are inactive precursor proteins until they are activated by double-stranded RNA synthesized during viral replication. As a result, these proteins are active in virus infected cells but not in uninfected cells.

Other Nonspecific Defenses

• Natural killer (NK) cells are lymphocytes that destroy cells infected by many different viruses (i.e., they are nonspecific). NK cells do not have an antigen receptor on their surface, unlike T and B lymphocytes. Rather, NK cells

recognize and destroy cells that do not display class I MHC proteins on the surface. They kill cells by the same mechanisms as do cytotoxic T cells (i.e., by secreting perforins and granzymes).

• Phagocytosis by macrophages and the clearance of mucus by the cilia of the respiratory tract are also important defenses. Damage to these defenses predisposes to viral infection.

• Increased corticosteroid levels suppress various host defenses and predispose to severe viral infections, especially disseminated herpesvirus infections. Malnutrition predisposes to severe measles infections in developing countries. The very young and the very old have more severe viral infections.

Specific Defenses

• Active immunity to viral infection is mediated by both antibodies and cytotoxic T cells. It can be elicited either by exposure to the virus or by immunization with a viral vaccine.

• Passive immunity consists of antibodies preformed in another person or animal.

• The duration of active immunity is much longer than that of passive immunity. Active immunity is measured in years, whereas passive immunity lasts a few weeks to a few months.

• Passive immunity is effective immediately, whereas it takes active immunity 7 to 10 days in the primary response (or 3–5 days in the secondary response) to stimulate detectable amounts of antibody.

• Herd immunity is the protection of an individual that results from immunity in many other members of the population (the herd) that interrupts transmission of the virus to the individual. Herd immunity can be achieved either by immunization or by natural infection of a sufficiently high percentage of the population.

Prevension

Because few drugs are useful against viral infections, prevention of infection by the use of vaccines is very important. Prevention of viral diseases can be achieved by the use of vaccines that induce active immunity or by the administration of preformed antibody that provides passive immunity.

Active Immunity

• Active immunity can be elicited by vaccines containing killed viruses, purified protein subunits, or live, attenuated (weakened) viruses.

• In general, **live viral vaccines are preferable to killed vaccines** for three reasons: (1) they induce a higher titer of antibody and hence longer-lasting protection; (2) they induce a broader range of antibody (e.g., both IgA and IgG, not just IgG); and (3) they activate cytotoxic T cells, which kill virus-infected cells.

• There are some potential **problems with live viral vaccines, the most important of which is reversion to virulence**. Transmission of the vaccine

virus to others who may be immunocompromised is another concern. Also there may be a second, unwanted virus in the vaccine that was present in the cells used to make the vaccine virus. This second virus may cause adverse effects.

• Live viral vaccines should not be given to immunocompromised individuals or to pregnant women.

• Vaccines grown in chick embryos, especially influenza vaccine, should not be given to those who have had an anaphylactic reaction to eggs.

Passive Immunity

• Passive immunity is immunity acquired by an individual by the transfer of preformed antibodies made in either other humans or in animals. These antibody preparations are often called **immune globulins**. Passive immunity also occurs naturally when IgG is transferred from the mother to the fetus across the placenta and when IgA is transferred from the mother to the newborn in colostrum.

• The main advantage of passive immunity is that it provides immediate protection. The main disadvantage is that it does not provide long-term protection (i.e., it is active only for a few weeks to a few months).

• Immune globulin preparations against rabies virus, hepatitis A virus, hepatitis B virus, and varicella-zoster virus are effective.

• Passive–active immunity consists of administering both immune globulins and a viral vaccine**.** This provides both immediate as well as long-term protection. For example, protection against rabies in an unimmunized person who has been bitten by a potentially rabid animal consists of both rabies immune globulins and the rabies vaccine.

Herd Immunity

• **Herd immunity** is the protection of an individual that results from immunity in many other members of the population (the "herd") that interrupts transmission of the virus to the individual. Herd immunity can be achieved either by active immunization or by natural infection of a sufficiently high percentage of the population. Herd immunity is unlikely to be achieved by passive immunity because, although antibodies can protect the individual against spread of virus through the bloodstream, they are unlikely to prevent viral replication at the portal of entry and consequent transmission to others.

Chemotherapy

Inhibitors of certain steps in viral replication can be used as chemotherapeutic agents to treat viral infections. In practical terms, it is much more important to inhibit the synthesis of viral nucleic acid than of viral proteins. The main obstacles involved are the low level of specificity of the agents in some cases (toxic effects because cellular metabolism is also affected) and the necessity of commencing therapy very early in the infection cycle.